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Filed : May 5, 1997

**REMARKS**

Claims 62-154 were pending in the application. By this response, claims 62, 66, 67, 79, 80, 85, 94, 95, 102, 123 and 128 have been amended while claims 63-65, 77, 78, 92, 93, 127, 129 and 130 have been canceled. No new claims have been added. Accordingly, claims 62, 66-76, 79-91, 94-126, 128 and 131-154 remain presented for examination.

Reexamination and reconsideration of the instant application is respectfully requested in view of the foregoing amendments and the following remarks. By this response, independent claims 62 and 123, directed to microbubble compositions comprising selected gas osmotic agents (GAOs) and selected GAO in combination with protein microshells respectively, have been amended to clarify that the incorporated modifier gas is a nonfluorocarbon gas. Specific support for these amendments may be found at page 14, lines 11-33, pages 24-30 and throughout the specification and Examples as filed. In addition claims dependent on these two claims have been amended or canceled to maintain the internal consistency of the claim set. Conversely the remaining independent claim, claim 109, directed to microbubble preparations comprising the vapor of a compound that is a liquid at 37°C has not be amended at this point. As will be discussed in more detail below, Applicants do not believe that the Unger and Yan et al. references constitute prior art under 35 U.S.C. §103 as set forth in the subject Official Action. Accordingly, Applicants submit that claim 109, and claims dependent thereon, are patentably nonobvious as filed. More generally, with the instant amendments and associated remarks, it is believed that all pending claims are allowable as presently written. Notice to that effect is respectfully requested.

**Personal Interview:**

Initially Applicants wish to thank Examiner Hollinden for the courtesy extended to their representative, Chris Dayton, during the personal interview of October 29, 1998. The substance of that interview is accurately reflected on the contemporaneous Examiner Interview Summary Record, and is further incorporated into the foregoing amendments and these remarks. The

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efforts of the Examiner directed to clarifying the scope of the present invention and analyzing the breadth and relevance of the cited art is particularly appreciated.

Entry of Preliminary Amendment:

In another matter, Applicants note that a second Preliminary Amendment, mailed June 19, 1998, apparently crossed in the mail with the instant Official Action. The Preliminary Amendment contained only additional dependent claims that recited particularly preferred embodiments of the present invention. Although this Preliminary Amendment was not specifically considered or addressed in the Official Action, it is believed that the foregoing amendments and following remarks are pertinent to the claimed subject matter of the June 19<sup>th</sup> filing. Moreover, it is believed that these dependent claims are allowable for the same reasons as the broader pending independent claims. As such, entry and allowance of these claims is requested.

Rejection of Claims Under 35 U.S.C. §103:

Turning now in detail to the instant Official Action, it is noted that all the previously pending claims were rejected under §103 as being unpatentable over Lambert et al. (5,552,133), Unger (5,705,187), Yan et al. (5,556,610) and Schneider et al. (5,413,774). More specifically, Lambert et al. is held to disclose protein encapsulated microbubbles while Schneider et al. is held to teach the substitution gases in the disclosed microbubble preparations. Additionally, Unger was held to disclose the use of compounds having a boiling point above 37° while Yan et al. purportedly discloses protein encapsulated microbubbles comprising more than one gas. Based on these references it was held that the claimed subject matter is not patentably distinguishable over the prior art and is properly rejected under §103. Applicants traverse this rejection.

With all due respect to the position set forth in the subject Official Action, it is submitted that those references which apparently constitute prior art under §103 fail to disclose a gas mixture comprising a gas osmotic agent and a nonfluorocarbon modifier gas or the use of a compound having a boiling point greater than about 37°C. Moreover, as discussed below,

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Applicants review of the cited references indicates that any disclosure of gaseous compounds having a boiling point greater than about 37°C in Unger is not entitled to a priority date that allows the subject matter to serve as basis for the instant rejection. Similarly, the subject matter in Yan et al. regarding the use of gas mixtures is not entitled to a priority date that allows it to function as a proper reference in the context of the subject rejection. Accordingly, Applicants submit that the instant rejection is effectively obviated and may properly be withdrawn.

As indicated above, Applicants have conducted a detailed review of the Unger file history and claims to priority and concluded that there was no disclosure regarding the use of gas mixtures comprising vapors of a compound that boils at 37°C that could be used to support a rejection of Applicant's pending claims. Rather, Applicants have concluded that the effective date of disclosure of the relevant subject matter is most likely that of April 5, 1995, the filing date of the Unger patent. This was the first disclosure in the relevant Unger patent family that gas mixtures comprising relatively high boiling compounds in a vaporous state could be used in microbubble compositions. Even with regard to the use of pure gaseous precursors in a liquid state, Applicants believe that Unger is clearly not entitled to a priority date of any earlier than November 30, 1993 which is the filing date of U.S. Patents 5,585,112 and 5,542,935, each cited in the claimed chain of priority. In this respect, Applicants note that the instant application is a continuation (as opposed to a CIP) of an application with an effective filing date of July 30, 1993. As such, Applicants submit that Unger does not provide a viable reference in conjunction with the instant rejection.

Nor does Yan et al. provide any support for the instant rejection. Initially, Applicants note that Yan et al. apparently fails to exemplify or disclose the use of high molecular weight compounds such as perfluorohexane. More significantly, a review of the reference shows that it is a continuation-in-part of the Schneider et al. patent cited in the instant action. Accordingly, while Yan et al. purportedly discloses the use of gas mixtures, it is submitted that the subject matter relevant to the instant rejection (i.e. gas mixtures and the use of fluorocarbon and nonfluorocarbon gases in combination) is clearly not entitled to any date earlier than the filing of the counterpart European application, i.e. December 15, 1993. Again, this date is not early

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enough for disclosed subject matter to constitute prior art with respect to an application having an effective filing date of July 30, 1993. Thus, it appears that Yan et al. may not be used as suggested in the instant Official Action to reject the presently claimed subject matter.

With regard to Schneider et al., Applicants have reviewed the patent and submit that it fails to fairly disclose mixtures of gases comprising a fluorocarbon gas osmotic agent and a nonfluorocarbon modifier gas. More specifically, the reference clearly fails to disclose the use of gas mixtures comprising the selected gas osmotic agents recited in pending claims 62 and 123 or the use of gas osmotic agents having a boiling point greater than about 37°C as recited in independent claim 109. In this regard, Applicants submit that "substituting gases" is hardly the same as providing a well characterized gaseous stabilization system comprising metered amounts of the individual components and designed to stabilize the microbubble over prolonged periods through an osmotic mechanism. Further, it is noted that Schneider et al. actually teach that it is desirable to "extensively purge" (Col. 8, lines 50-57) the microbubble composition with the new gas prior to storage. Essentially, this results in the introduction of a substantially pure atmosphere of the selected gas rather than a gas mixture such as that required by the amended claims. As such, Applicants submit that Schneider is actually teaching away from the present invention which advantageously employs gas mixtures for osmotic stabilization. Nor does the reference provide any indication that such osmotically balanced gases may be advantageously combined with protein microshells as is recited in claim 123. Accordingly, it is submitted that Schneider et al., either alone or in combination with other references, cannot fairly suggest the presently claimed invention.

Lastly, the previously pending claims were rejected over Lambert et al. which arguably discloses the use of protein microspheres. However, the reference fails to suggest that gaseous mixtures comprising the selected gas osmotic agents and nonfluorocarbon modifier gases could provide the long lasting stabilization systems afforded by the instant invention. Rather, the reference merely discloses that various compounds may be combined with no indication as to the ultimate composition of the resulting blend. In this respect, the reference actually teaches that air (a "combination" of gases) may provide the desired stabilization. Clearly, such a broad, but

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rational, interpretation of the cited passage cannot render the presently claimed invention, which requires gaseous mixtures comprising highly selective gas osmotic agents, obvious. Thus, it is submitted that Lambert et al. does not teach or suggest the instant invention as presently claimed.

In addition to the shortcomings inherent in the individual references, Applicant submits that, absent hindsight, there is absolutely no motivation to combine the references as suggested in the Official Action. As stated by the courts:

“Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so.” (quoting *ACS Hosp. Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). . . . The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.<sup>1</sup>

In the instant case, it appears that both Yan et al. and Unger do not provide the disclosures necessary to support the instant rejection. With regard to Schneider et al. and Lambert et al., neither reference provides any indication that selected gas osmotic agents, some with boiling points greater than 37°C, could be advantageously combined with nonfluorocarbon modifier gases to produce Applicant’s stabilization system. Further, as discussed above, even if the references were combined as suggested they would not provide the claimed methods. Accordingly, the rejection is respectfully traversed as the cited references do not provide a basis for the establishment of a *prima facie* case of obviousness.

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<sup>1</sup> *In re Fritch*, 23 USPQ 2d 1780, 1783-84 (Fed. Cir. 1992).

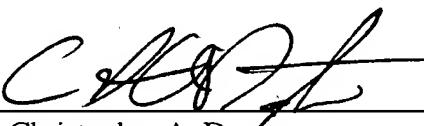
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Conclusion:

In view of the present amendments and associated remarks, reconsideration and allowance of all the pending claims is respectfully requested. Please continue to send all correspondence to Knobbe, Martens, Olson & Bear at the address of record. However, the Examiner is invited to telephone the undersigned attorney at the number below if it is believed that this will expedite prosecution of the present application.

Respectfully submitted,

Dated: 12/22/98

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